Amendments to the Specification:

Please delete the paragraph at page 2, line 1 and replace it with the following amended paragraph:

More recent and better controlled variants of this technique employ temperature-sensitive oncogenes. This approach permits the in vitro proliferation of the cells under the "permissive" temperature. The non-permissive temperature is chosen to equal the body temperature, resulting in instability of the gene product and ceasing of proliferation after transplantation (Renfranz et al., Cell 66:713-729, 1991). However, the ~~oncogen~~**oncogene** remains in the transplanted cells, and low activity or reactivation at a later time point cannot be entirely excluded. Newer strategies have been aiming at the removal of the oncogene after completion of the proliferation phase, using molecular biological tools (Westerman & Leboulch, Proc. Natl. Acad. Sci. USA 93:8971-8976, 1996). As all cell lines, ~~oncogen~~**oncogene**-immortalized precursor cells exhibit a high susceptibility to chromosomal aberrations.

Please delete the paragraph at page 2, line 33 through page 3, line 20, and replace it with the following amended paragraph:

Embryonic stem cells (ES cells) provide entirely new perspectives for the generation of donor cells for transplantation. ES cells were first described in mice in 1981 (Martin, Proc. Natl. Acad. Sci. USA 78:7634-7638, 1981; Evans & Kaufman, Nature 292:154-156, 1981). They can be derived, for example, from the inner cell mass of ~~3,5-day-old embryos~~**3.5-day-old embryos**. ES cells are pluripotent and can generate all tissues and cell types. This is best reflected by the fact that ES cells injected into another blastocyst can participate in the generation of all tissues including the germ line, thereby yielding chimeric animals (Bradley et al., Nature 309:255-256, 1984). A unique feature of ES cells is the fact that in the presence of leukemia inhibitory factor (LIF) they can be maintained and proliferated in a pluripotent stage (Smith et al., Nature 336:688-690, 1988). Today, this is frequently exploited for the genetic modification of ES cells. Blastocyst injection of these engineered ES cells is then used to generate transgenic animals (Robertson et al., Nature 323:445-448, 1986). Less frequently, ES cells have been used for in vitro differentiation studies. This technique permits the study and experimental manipulation of early tissue development under controlled conditions in vitro. Meanwhile, pluripotent embryonic stem cells have been isolated from a large variety of species including rat (Iannaconne et al., Dev. Biol. 163:288-292, 1994), hamster (Doetschman et al., Dev. Biol. 127:224-227, 1988),

birds (Pain et al., Development 122:2339-2348, 1996), fish (Sun et al., Mol. Mar. Biol. Biotechno. 4:193-199, 1995), swine (Wheeler, Reprod. Fertil. Dev. 6:563-568, 1994), cattle (First et al., Reprod. Fertil. Dev. 6:553-562) and primates (Thomson et al., Proc. Natl. Acad. Sci. USA 92:7844-7848, 1995). Several months following the submission of the German patent application No. 197 56 864.5 two research teams succeeded in isolating ES cells and ES cell-like stem cells from embryonic human tissue (Thomson et al., Science 282: 1145-1147, 1998; Shamblott et al., Proc. Natl. Acad. Sci. USA 95: 13726-13731, 1998). Other recent studies indicate that embryos and embryonic stem cells can be generated by transplanting nuclei from embryonic and mature mammalian cells into enucleated oocytes (Campbell et al., Nature 380:64-66, 1996; Wilmut et al., Nature 385:810-813, 1997).

Please delete the paragraph at page 4, line 21, and replace it with the following amended paragraph. Corrections are made relative to the previous amended version of the paragraph.

The generation of sufficient numbers of defined neural precursor cells is currently one of the key problems in neural transplantation. At present, precursor cells are isolated from the embryonic mammalian brain. For example, material from up to seven human embryos is required for transplantation of an individual Parkinson patient. Such a strategy is associated with severe problems and cannot be used to treat large numbers of Parkinson patients in the long term. Efforts to proliferate neural cells ~~in vitro~~***in vitro*** prior to transplantation have, so far, ~~not lead to~~**not led to** significant improvements. Oncogene-mediated immortalization bears considerable risks due to the introduction of a tumorigenic gene into the donor cells. The order of magnitude of growth factor-mediated proliferation of precursor cells is not sufficient for a potential clinical application. In addition, the ability of expanded cells to incorporate into the host tissue is currently unclear.

Please delete the paragraph at page 7, line 24, and replace it with the following amended paragraph:

Glial cell of the nervous system. The most important known function of these cells is the insulation of nerve cell processes (axons). Axons are insulated by a sheath of myelin generated by the ~~oligodendrocytors~~**oligodendrocytes**. Defects in myelin formation result in demyelinating diseases. One of the most frequent demyelinating diseases is multiple sclerosis (MS).

Please delete the line at page 9, line 5, and replace it with the following amended line:

(b') culturing of the ES cells from (a') to a neural precursor cell stage

Please delete the paragraph at page 9, line 32 through page 10, line 2, and replace it with the following amended paragraph:

Preferred applications include the reconstitution of neuronal cells damaged or lost as **a** result of traumatic, ischemic, degenerative, genetic, hypoxic, metabolic, infectious, neoplastic or toxic disorders of the nervous system. Particulary preferred is the reconstitution of neural cells in traumatic lesions of the brain and spinal cord, ischemic and hemorrhagic infarctions, Parkinsons disease, Huntingtons disease, Alzheimers disease, hereditary atrophic disorders of the cerebellum and brain stem, motoneuron diseases and spinal muscular atrophies. Preferred applications further include the reconstitution of neuronal cells lost or damaged due to age-related changes. A particularly preferred application is the remyelination of demyelinated areas of the nervous system, particularly in diseases such as multiple sclerosis (MS), adrenoleukodystrophy and Pelizeaus-Merzbacher disease.

Please delete the paragraph at page 14, line 27 through page 15, line 2, and replace it with the following amended paragraph:

More recent studies indicate that embryos and embryonic stem cells can be generated by transplanting nuclei from ~~cells of an~~**cells of a** mature ~~individuum~~**individual** into enucleated oocytes (Wilmut et al., Nature 385:810-813, 1997). For the specialist it is obvious that a combination of such nuclear transfer strategies with the invention described herein permits the generation of autologous neural precursor cells from differentiated cells of the same ~~individuum~~**individual**. The generation of embryos through transfer of nuclei from mature cells into enucleated oocytes has been applied to large mammals such as sheep (Wilmut et al., Nature 385:810-813, 1997) and is, therefore, also applicable to humans. ES cells or ES cell-like cells may also be obtained from embryonic germ cells. Studies published after the priority date of this patent application show that human ES cells can be isolated from human blastocysts (Thomson et al., Science 282: 1145-1147, 1998), and human ES cell-like cells can be obtained from human primordial germ cells (Shamblott et al., Proc. Natl. Acad. Sci. USA 95: 13726-13731, 1998). These studies indicate that the methods described in this patent application, alone or in combination with nuclear transfer strategies, can also be applied to humans.

Please delete the paragraph at page 17, line 6, and replace it with the following amended paragraph:

During the last couple of years numerous factors have been identified which influence the differentiation of neuronal cell populations. These factors may, for example, lead to polarization within neural tissue. For example, it was shown that the product of the gene Sonic hedgehog induces a ventral phenotype in neural tissue (Ericson et al., Cell 81:747-756, 1995). It is to be expected that such factors also influence the differentiation of neural cells generated ~~artoficially~~**artificially** from ES cells. For the specialist it is obvious that the application of such factors will permit the generation of neurons and glial cells with specific phenotypes. For example, induction of a ventral mesencephalic phenotype may yield cells suitable for transplantation into Parkinson patients. In cultured fragments of neural tissue it has already been shown that Sonic hedgehog can induce dopaminergic ventral mesencephalic neurons (Wang et al., Nature Med. 1:1184-1188, 1995).

Please delete the paragraph at page 18, line 16, and replace it with the following amended paragraph:

The methods described herein may further be combined with established cell separation cell sorting procedures. For example, neural subpopulations may be separated at defined time points using fluorescent-activated cell sorting (FACS), immunopanning, or similar methods. A ~~detailed~~**detailed** sorting and subclassification may permit the generation of replacement cells (including genetically modified replacement cells) tailored to the individual patients needs. Since both ES cells and the ES cell-derived neural precursor cells described herein can be frozen and thawed without loosing their properties, it is possible to establish cell banks, including autologous cell banks.

Please insert a blank line between the paragraph ending at page 27, line 19 and the paragraph beginning at page 27, line 20, in order to indicate that there are two separate paragraphs.

Please delete the paragraph at page 27, line 20 and replace it with the following amended paragraph:

For transplantation, pregnant rats were anesthetized by intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg) at day 16 or 17 of gestation. Following laparotomy, individual embryos were identified under transillumination with a fiber optic light source. The donor cells were loaded in a small glass capillary (pore size 50-100 µm), and the capillary was advanced through the uterine wall and the embryonic skull into the lateral ventricle of the recipient embryo as described (Brüstle et al., Current Protocols in Neuroscience, John Wiley, New York, 1997). Two to nine µl of the cell suspension (containing 100.000 to 900.000 cells) were injected into the ventricular system. Following transplantation of several or all embryos, the abdomen was closed with surgical sutures and the mother animal left for ~~spontaous~~**spontaneous** vaginal birth. Since myelin-deficiency in this animal model is an X-linked recessive disorder, approximately 50% of the male pups are affected. Affected animals develop strong tremor by the third week of age and usually die within their fourth postnatal week.

Please delete the paragraph at page 27, line 34 through page 28, line 31, and replace it with the following amended paragraph:

4.3. Histological analysis of the transplant recipients

In order to detect donor-derived myelin formation, recipient animals were anesthetized in the third or fourth postnatal week and transcardially perfused with 4% paraformaldehyde (Sigma No. P-6148) in PBS according to standard methods. The brains were removed from the skull, postfixed overnight at 4°C in the same fixative and subsequently cut in 50 µm sections using a vibratome. Donor cells were detected by DNA in situ hybridization with a probe to mouse satellite DNA (Hörz & Altenburger, Nucl. Acids Res. 9:683-696, 1981; Brüstle et al., Neuron 15:1275-1285, 1995). Donor cell-derived myelin was visualized with antibodies to myelin proteins such as myelin basic protein (MBP; Boehringer No. 1118099) or proteolipid protein (PLP; a gift from Ian Griffiths, Department of Veterinary Clinical Studies, University of Glasgow, Bearsden, Scotland). Sections labeled with antibodies to myelin proteins were subsequently subjected to DNA in situ hybridization with a probe to mouse satellite DNA (Brüstle et al., Neuron 15:1275-1285, 1995). This double labeling procedure permits unequivocal indentification of donor cell-derived myelin. The experiments showed that donor cells implanted into the ventricle migrate into a large variety of telencephalic, diencephalic and mesencephalic brain regions (14 analyzed recipient animals). Hybridized cells were found, e.g., in cortex, hippocampus, septum, striatum, bulbus olfactorius, thalamus, hypothalamus, tectum, cerebellum as well as in the corpus callosum, anterior commissure, tractus opticus and the optic nerve. No space-occupying clusters of donor cells were observed after transplantation into the ventricular system. Out of 35 transplanted embryos, 11 male pups exhibited symptoms of myelin deficiency. Eight of these had received successful intraventricular transplants. In six out of these eight animals, donor-derived myelin formation was verified by double labeling of hybridized cells with MBP or PLP-antibodies. In the remaining 2 animals, the number of incorporated cells was too low for a reliable evaluation of donor-derived myelin formation by double labeling procedures. However, immunohistochemical screening of sections from these animals with the mouse-specific antibody M2 (Zhou et al., J. Comp. Neurol. 292:320-330, 1990) also showed incorporated donor-derived glial cells in the host tissue. Donor-derived myelin formation was most pronounced in fiber tracts such as the corpus callosum, the anterior commissure and commissural fibers in tectum. In addition, myelinating donor cells were detected in gray matter regions such as cortex, septum, thalamus, hypothalamus and tectum. Seven out of eight successfully transplanted animals also showed incorporated ES cell-derived

astrocytes. Donor-derived astrocytes were detected by ~~immunohistochmistry~~**immun histoch mistry** with antibodies to the mouse-specific antigens M2 (Zhou et al., J. Comp. Neurol. 292:320-330, 1990) and M6 (Lund et al., Neurosci. Lett. 61:221-226, 1985) or by double labeling of cells hybridized with a mouse-specific DNA probe with an antibody to glial fibrillary acidic protein (GFAP; ICN No. 69-110).